DIABETES AND PORTACAVAL ANASTOMOSIS: A PROSPECTIVE CONTROLLED STUDY

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BY

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D.M.R.

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INTRODUCTION

In recent years several authors have reported the appearance of diabetes after construction of portacaval anastomosis (PCA) in patients with hepatic cirrhosis.(1-4) Seven cases have been reported in which diabetes appeared from five to 19 months after creation of a PCA. (Table 1)

Recently much evidence has been published calling attention to the too frequent coexistence of diabetes and hepatic cirrhosis. A number of investigators have reported the presence of diabetes in 11-35% of their patients with cirrhosis. (5-13)

A number of features commonly associated with chronic liver disease, especially Laennec's cirrhosis, might be responsible for the diabetes seen in cirrhosis. Theoretically, one might expect to see several different pathogenetic types of diabetes. Some of these may be classified as follows:

<u>Hepatogenous Diabetes</u> Injury to hepatic parenchymal cells might lead to altered carbohydrate metabolism. Both hyperglycemia and hypoglycemia have been observed in chronic hepatic injury presumably secondary to impaired glucogenesis and glycogenolysis respectively. Conn and Newbergh have observed hypoglycemia and impaired glucose tolerance in patients with chronic cholangitis. (14) A reversible transient diabetic state has been described

by Leevy in patients with fatty infiltration of the liver secondary to alcoholism which disappeared with improvement in liver function and recurred with resumption of alcohol ingestion. (15)

Pancreatitic Diabetes Pancreatitis, often silent, is a well known concomitant of alcoholic cirrhosis. It has been estimated to be present in one-third of cirrhotic patients. (16) It has also been observed that acute pancreatitis may be associated with transient diabetes, (17) and that chronic pancreatitis can result in permanent decrease in insulin secretory capacity secondary to beta cell injury.(18) Diabetes may thus develop in cirrhotic patients as a consequence of inflammatory injury to the islet cells, i.e. not actually as a result of the liver disease per se.

Hemosiderotic Diabetes Diabetes is one of the traditional components of idiopathic hemochromatosis. It is thought to be secondary to the deposition of excess hemosiderin in the islet cells. While the syndrome of idiopathic hemochromatosis does not appear very often in alcoholic cirrhosis, increased hepatic iron deposition is common in this disease.(19) Pancreatic hemosiderin deposition while much less common in cirrhosis occurs with sufficient frequency to warrant serious consideration as a cause of diabetes. Furthermore, full blown hemo-

chromatotic syndrome has been shown to occur shortly after construction of a portacaval shunt.(20)

<u>Insulin-resistant Diabetes</u> Insulin resistance has been demonstrated to occur in cirrhosis.(21) Megyesi suggested that chronic hepatic disease produces endogenous insulin resistance and hyperinsulinism which may eventually lead to beta cell exhaustion and insulin deficiency.(22) Samaan observed that cirrhotic patients with normal or slightly abnormal glucose tolerance showed a greater hyperinsulinemic response to oral glucose administration than cirrhotics with grossly abnormal glucose tolerance. He interpreted this insulin resistance to be the key defect in the development of diabetes and implied that patients may develop diabetes when they are no longer able to satisfy the increasing demand for insulin.(23) The cause of the insulin resistance is not evident but might be related to elevated free fatty acids which are present in cirrhosis,(24,25) or to hypersomatotropism.

<u>Somatotropic Diabetes</u> Acromegaly is associated with increased frequency of diabetic carbohydrate intolerance and peripheral insulin resistance. Administration of exogenous growth hormone may induce these abnormalities.(26) Growth hormone has been shown to be elevated in some cirrhotic patients.(27) It is conceivable that hyper-

somatotropism may precipitate diabetes in susceptible patients with cirrhosis. No cause for the elevated growth hormone levels has been identified.

Kaliopenic Diabetes Potassium depletion has been shown to be a predisposing factor in the development of diabetes. It has been observed that approximately 50% of patients with primary aldosteronism have impaired glucose metabolism. This defect in carbohydrate metabolism has been reversed by either removing the tumor or replacing potassium losses.(28) Patients with alcoholic cirrhosis almost always have a sizeable potassium deficit due to a combination of factors among which are poor dietary intake, fluid losses from vomiting and diarrhea, potassium losing diuretics, and coincidence of secondary aldosteronism.(29) Thus secondary aldosteronism, like primary aldosteronism, through its associated potassium depletion, may precipitate diabetes.

Genetic Diabetes A certain percentage of any group of patients will have a genetic predisposition toward the development of diabetes, and will go on to develop the disease in the absence of any secondary precipitating factors. It has been shown that there is a greater genetic predisposition to the development of diabetes among cirrhotic patients than that which would be found in the general population.

The appearance of diabetes after PCA has been an inconstant observation. It has been reported that no significant changes in carbohydrate metabolism can be found in cirrhotic patients after PCA.(31) Several studies dealing with the purely surgical aspects of PCA dealing with large numbers of patients have only casually mentioned diabetes as a complication of PCA.(32-34)

Most of the data relating diabetes to PCA are in the form of retrospective observations. A common definition of diabetes is lacking, and in many cases the criteria used in making the diagnosis of diabetes are not specified. No controlled study of this association has been reported. In most reports consideration of the potentially diabetogenic factors found in cirrhosis is not seen.

The present study was performed to determine in a prospective, controlled fashion, whether or not PCA increases the incidence of diabetes, and if so to attempt to elucidate contributing pathogenetic mechanisms. The patients included in several ongoing, prospective investigations of prophylactic PCA provided an ideal group of patients in which to evaluate these phenomena.

MATERIALS AND METHODS

The patients used in this investigation were those patients studied by Conn and Lindenmuth in their controlled prospective investigations of prophylactic portacaval anastomosis in the treatment of cirrhotic patients with esophageal varices.(35,36) These studies were undertaken to determine the effect of PCA on long term survival of patients with cirrhosis and esophageal varices who had not previously bled from their varices. All patients included in these studies satisfied strict criteria for admission, and once included, were randomized into separate groups, one of which served as control for the other group which had portacaval sunt operations. Thus im planning such a study there are two groups of patients whose only apparent difference is that one had the operative procedure while the other did not.

The studies were conducted as two separate investigations over a period of 13 years. The patients studied were all men who had been admitted to the West Haven Veterans Administration Hospital (WHVAH). Prophylactic Shunt Study I (PSS-I) included patients admitted between September 1, 1958 and June 1, 1963. The criteria for admission to this study were as follows:

1) a histologic diagnosis of cirrhosis.

2) esophagoscopic demonstration of esophageal varices.

3) splenic pulp pressure exceeding 200 mm. H_2O.

4) no previous history of hemorrhage from varices.

5) patients had to be considered good operative risks.

During this period approximately 250 cirrhotic patients were admitted to the hospital. Of the survivors who had not previously bled from varices, 68 were shown to have esophageal varices. Eight were considered poor operative risks and were excluded from the study because of severe non-hepatic disorders such as cardiovascular decompensation and pulmonary insufficiency. These patients constitute the Exclusion Group I. No patients were excluded from the study because of the severity of their liver disease.

The remaining 60 patients were selected for inclusion in the clinical trial. After inclusion each patient was chosen by random selection to have a portacaval shunt or to be an unoperated control patient. Control Group I consists of 31 patients chosen to be control patients. Twenty-nine were chosen to have portacaval anastomoses. Four refused and comprised Refusal Group I. The remaining 25 patients constitute Shunt Group I. End-to-side portacaval anastomoses were constructed in 21, and side-to-side anastomoses in four.

This investigation (PSS-I) showed that survival

was not increased by prophylactic PCA. It was observed however, that all patients who bled from varices in this study had had overt ascites at the time of inclusion. Consequently a second study was undertaken of cirrhotic patients with varices and ascites. Prophylactic Shunt Study-II (PSS-II) included patients admitted from January 1, 1965 to December 31, 1970. The criteria for admission to PSS-II are similar to those of PSS-I:

1) a histologic diagnosis of cirrhosis.
2) esophagoscopic demonstration of esophageal varices.
3) splenic pulp pressure exceeding 250 mm H_2O at time of inclusion.
4) no previous history of hemorrhage from varices.
5) patients had to be considered good operative risks.
6) patients must have had overt ascites, defined as abdominal distension accompanied by shifting flank dullness of at least 8 cm. during the hospital admission; a history of prior ascites must have been documented by paracentesis or other unequivocal proof.
7) patients who had reached their sixty-fifth birthday were excluded in order to mi imize the incidence of portal-systemic encephalopathy

which occurs most commonly in elderly patients.

Approximately 360 new patients with cirrhosis were admitted to the WHVAH during the time of PSS-II. Of 102 cirrhotic patients with esophageal varices who had not previously bled from varices, 26 were excluded (Exclusion Group II), 9 on the basis of age, 7 because of splenic pulp pressure levels less than 250 mm. H_2O, 2 with severe portal-systemic encephalopathy, and 8 with severe non-hepatic disorders which made them poor operative risks. Thirty-three who did not have ascites comprise the Non-Ascitic Group. Forty three satisfied all criteria for admission and were randomized. Twenty-two were selected to have prophylactic portacaval shunts. Two refused and constitute Refusal Group II. Portacaval shunts were performed in the remaining 20 (Shunt Group II). Twenty-one patients comprise Control Group II.

The various groups of patients were similar in age, in the duration of symptoms of cirrhosis, in the type and severity of cirrhosis, in liver function, and in the physical signs of cirrhosis.(Tables 2-7 and Figures I-2) Ascites had been present in about two thirds at the time of inclusion. The splenic pulp pressures and ammonia tolerance test were similar in the Control and Prophylactic Shunt Groups. The magnitude of varices, determined endoscopically was similar in the two groups.

One additional group of patients was also studied. This group includes 48 patients from the WHVAH who had bled previously from esophageal varices and were therefore not eligible in the prophylactic portacaval shunt study. These patients all of whom had a histologic diagnosis of cirrhosis, had therapeutic portacaval shunts performed and comprise the Therapeutic Portacaval Shunt Group. Therapeutic shunt patients are included to provide data on an additional group of portacaval shunts performed at this hospital. The similarity between the prophylactic and therapeutic shunt patients with regard to age, severity of cirrhosis, including physical signs and liver function tests permits combination of these groups.

The charts of all patients were reviewed and the following information extracted:

1) age, sex, and history of diabetes in the immediate family (siblings, parents or grandparents).
2) etiology of cirrhosis,
3) date of initial appearance of signs of cirrhosis.
4) liver function tests before and after inclusion or shunt.
5) physical signs of cirrhosis before and after inclusion or shunt.
6) splenic pulp pressure.
7) history of alcohol intake including the nature

of the beverage imbibed in the greatest amount.

8) presence of pancreatitis as determined by serum amylase and lipase activity and autopsy findings.

9) presence of hemochromatosis or any iron storage disorder as determined from clinical findings as well as serum iron, iron binding capacity, and iron deposition in liver, bone marrow and other tissues at biopsy and/or autopsy.

10) fasting serum glucose levels before and after inclusion in control patients, and before and after shunt for operated patients. In most cases many fasting glucose levels were recorded at frequent intervals after inclusion and throughout follow-up periods as well as before inclusion, for every hospital admission in the chart.

11) results of glucose tolerance tests, urinalyses for glycosuria, both before and after inclusion or shunt.

Additional data gathered on patients classified as having diabetes included

12) date of initial recognition of diabetes.

13) therapy employed in treatment of diabetes.

Diagnosis of Diabetes . Diabetes was defined as persistent fasting hyperglycemia, all serum glucose levels

greater than 140 mg./ 100 ml. (AutoAnalyzer ferricyanide method). Each patient so classified must have had at least two such analyses each of which was greater than 140 mg./ 100 ml. Glucose tolerance tests were not used as diagnostic criteria since oral glucose toleramce has been shown to be abnormal in the majority of cirrhotic patients.(37)

Chi square statistical analyses were all performed using Yates correction.

RESULTS

Incidence of Diabetes at Inclusion. (Tables 8-10)

A total of 214 patients were studied of whom 20 (9.2%) had diabetes as defined previously.

Non-shunt Patients at Time of Inclusion. At inclusion in Control Group I, 31 patients were studied, of whom 2 (6.5%) had diabetes. Of 21 patients in Control Group II, 1 (4.7%) had diabetes. The difference between these two groups is not statistically significant ($p > 0.5$). Consequently the two control groups have been combined into a single control group (Control Group I-II). A total of 69 other non-operated patients assigned to Exclusion Groups I-II, Refusal Groups I-II, and Non-Ascitic Group, were united into the Combined Exclusion Group. Seven of these 69 patients (10.2%) had diabetes. The incidence of diabetes at the time of inclusion in Control Group I-II and the Combined Exclusion Group did not differ significantly. Therefore they have been combined into the single Non-Operated Group which consists of 121 patients, 10 of whom (8.3%) had diabetes at the time of inclusion.

Shunt Patients at Time of Inclusion. At the time of inclusion Shunt Group I included 25 patients, none (0%) of whom had diabetes. Shunt Group II included 20 patients, of whom 3 (15%) had diabetes. The difference between these two groups is not significant statistically. The two shunt

groups have been combined into Shunt Group I-II, which includes 45 patients at inclusion of whom 3 (6.6%) had diabetes.

At inclusion, 8 (16.7%) of 48 patients in the Therapeutic Shunt Group had diabetes. The frequency of diabetes in this group was slightly higher, but not significantly higher, than in Shunt Group I-II ($p > 0.05$). The two have been combined to form a single Operated Group which consisted at the time of inclusion of 93 patients of whom 11 (11.8%) had diabetes.

Comparison of the Frequency of Diabetes in Operated vs. Non-Operated Groups at Time of Inclusion. At the time of admission to the study therefore, there were 121 patients in the Non-Operated Group of whom 10 (8.3%) had diabetes compared with 93 in the Operated Group of whom 11 (11.8%) had diabetes. This difference is not significant statistically.

Incidence of Diabetes during Follow-up. (Tables 8-10)

Of 214 patients included at the beginning of the study 175 (82%) were followed for at least 6 months. Almost all of those not followed were patients who died within 6 months of inclusion into the study. Of the 175 patients so followed, 18 (10.3%) had diabetes at the time of inclusion.

Diabetes was present at inclusion in 8 of the 103 (7.8%) Non-Operated patients. Similarly the prevalence

of diabetes was 12.5% (10 of 72) in the Operated Group.

The 103 patients in the Non-Operated Group were followed for an average of 44.5 months (range, 6 to 147 months). At the end of the period of observation, 16 (15.5%) had diabetes. Thus, 8 additional patients had developed diabetes during this period.

The 72 patients in the Operated Group were followed for an average of 39.8 months.(range, 6 to 141 months). At the end of the study 21 (37.8%) had diabetes. Eleven additional patients had developed diabetes during the period of observation.

If one compares the new cases of diabetes which appeared during the period of follow-up, (8 of 95 at risk* in the Non-Operated Group vs. 11 of 62 at risk in the Operated Group) the difference is not significant statistically. ($\chi^2 = 1.75$ $p > 0.05$)

At the end of the study, 16 of 103 patients (15.5%) in the Non-Opezated Group had diabetes as did 21 (29%) of 72 in the Operated Group. The difference between these two groups is statistically significant. ($\chi^2 = 3.94$ $p < 0.05$)

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* Of 103 patients in the group, 8 had diabetes at inclusion, Therefore only 95 (103-8) were at risk of developing diabetes during follow-up.

Comparison of Features of Cirrhosis in Operated and Non-Operated Groups at Time of Inclusion.

As seen in Table 11 the Non-Operated Group did not differ significantly from the Operated Group in the clinical features of cirrhosis at the time of inclusion. In both groups the etiology of cirrhosis was almost exclusively alcoholic. The mean age of non-operated patients was 51.0 years, and that of operated patients was 50.5 years. Physical findings and laboratory values at the time of inclusion were similar. Practically all had hepatomegaly. Approximately half were jaundiced and two thirds had spider angiomata. About two thirds also had ascites. Liver function tests were also similar in the groups. The mean serum albumin levels were 2.8 gm./100ml. in the Non-Operated and 3.0 gm./100 ml. in the Operated Group. Mean SGOT levels were 52.0 and 47.5 Reitman-Frankel units respectively. Alkaline phosphatase levels were similar in the two groups.

A positive family history of diabetes in the immediate family was found in 15 patients (14.6%), in thethe Non-Operated Group, and in 20 (27.8%) im the Operated Group. This difference is significant statistically (χ^2=3.84 $p < 0.05$).

Comparison of Features of Cirrhosis in Diabetic and Non-Diabetic Patients.

Comparing all diabetic patients in this study with all non-diabetic patients, we see in Table 12 that in most respects the two groups are similar. The mean age at inclusion is similar. Physical signs of cirrhosis and liver function studies were also similar in diabetic and non-diabetic patients.

A positive family history of diabetes in the immediate family was noted in 12 (31.4%) of diabetics and in 25 (18.1%) of non-diabetics. This difference is not significant ($\chi^2 = 2.78 \quad p > 0.05$)

Appearance of Pancreatitis and Hemosiderosis in the Various Groups. (Table 14)

Pancreatitis was found in 4 (3.9%) of Non-Operated Group patients and in 6 (8.3%) of the Operated Group. This difference is not significant. Excessive hepatic hemosiderin deposits were found in 3 (2.9%) of non-operated patients and 4 (5.6%) of operated patients. Again, this difference is not significant .

Comparing diabetic and non-diabetic patients we find that pancreatitis was present in 2 (5.4%) of diabetic patients and in 8 (5.8%) of non-diabetics. This difference is not significant.

Hepatic hemosiderosis was found in 4 (10.8%) of

of 37 patients compared with only 3 (2.2%) of non-diabetic patients. This difference is significant ($\chi^2 = 3.64$ $p < 0.05$).

DISCUSSION

The evidence here suggests that there is a relationship between the surgical creation of a portacaval anastomosis and the development of diabetes. The data are derived from two groups of cirrhotic patients similar in nearly all respects, including the prevalence of diabetes, before surgical intervention. At the conclusion of the period of observation, diabetes was more common in the operated patients. These most interesting observations raise a number of questions, the answers to which might help to explain the pathogenesis of the diabetes of cirrhosis.

Diabetes mellitus is a generalized chronic metabolic disorder which usually develops in subjects with a hereditary predisposition, and is manifested in its fully developed form by weakness, lassitude, loss of weight, and by hyperglycemia, glycosuria, ketosis, acidosis, and protein breakdown. Secondary abnormalities of small blood vessels may appear, and ultimately cause renal failure, blindness, neuritis, hypertension, and congestive heart failure.

Current classification divides diabetes into a primary type of unknown cause, and an acquired secondary type.(38) Primary diabetes is the more common of the two. It is a familial disorder characterized by abnormal carbohydrate metabolism and degenerative vascular disease, resulting from a relative or absolute insulin

deficiency. It is a relatively stable disease which usually occurs in overweight individuals, and may exist for long periods of time without symptoms. Although they have a mild form of the disease they are relatively resistant to insulin, but paradoxically usually do not require exogenous insulin therapy, and will on most cases remain stable on dietary therapy alone, rarely developing ketosis.

Secondary diabetes is considered to be an acquired form of the disease in which alterations exist that mimic the primary state, but which are secondary to an organic dysfunction which becomes responsible for a relative or absolute insulin deficiency. These various etiologies have been classified as follows:

1) Hyperadrenalism. cortical- as see in Cushing's syndrome and primary aldosteronism; and medullary- as seen in pheochromocytoma. Although hepatic corticosteroid metabolism is decreased in patients with liver disease, endogenous production by the adrenals tends to slow, presumably to maintain normal circulating levels. (39)
2) Hyperpituitarism. acromegaly, pituitary basophilism, and therapy with adrenocorticotropic hormone and somatotropin as examples.
3) Hyperthyroidism. evidenced by thyrotoxicosis

thyroid therapy which are rare causes of clinical diabetes. We have found neither clinical signs nor laboratory evidence of hyperthyroidism in our cirrhotic patients.

4) Destruction of islet cell tissues as seen in hemochromatosis, pancreatitis, cystic or neo-plastic pancreatic disease and surgical removal of pancreatic tissue.

The acquired type of diabetes is not nearly as likely to produce degenerative changes, and when it does, these are much less advanced than those commonly found in the primary form of the disease. Patients with secondary diabetes as a rule have a lower incidence of a positive family history of diabetes. This form of the disease is frequently associated with remission and if it is practicable to remove the cause of secondary diabetes, e.g. cessation of cortocosteroid therapy, a cure of the diabetes may be anticipated.

The diagnosis of diabetes may be suspected through recognition of the common clinical signs associated with it and confirmed through a number of laboratory determinations. Abnormal glucose tolerance may be recognized before the clinical appearance of diabetes and before persistent elevation of fasting blood glucose levels. As mentioned previously, oral glucose tolerance is abnormal in the

majority of non-diabetic cirrhotic patients.(37) Although the mechanism of the impaired glucose tolerance is not known, it is probable that the conventional diagnostic criteria for diabetes are not applicable to cirrhotic patients. We have arbitrarily decided, therefore, that the oral glucose tolerance test is unsuitable as a diagnostic criterion for our purposes, and have defined diabetes as persistent fasting serum glucose levels greater than 140 mg./100 ml. (this is equivalent to approximately 120 mg./100 ml. for whole blood determinations). By choosing these more rigid criteria we have insured that only severe disturbances of glucose metabolism will be classified as diabetes.

<u>What Type of Diabetes is Found in Chronic Liver Disease?</u>

Many observers have reported an increased incidence of diabetes in patients with cirrhosis.(5-13) There is evidence for both the primary and secondary types of diabetes in such patients. Conn in 1969 observed diabetes as defined by fasting hyperglycemia greater than 140 mg./100 ml. (serum) in 16.7% of 240 patients with predominantly alcoholic cirrhosis, as opposed to 7% of a random sample of non cirrhotic patients in the same hospital.(5) He observed that 46% of the cirrhotic-diabetic patients had a positive family history of diabetes in the immediate family. He also noted that among cirrhotic patients

without diabetes the incidence of a positive family history was 16% which is far higher than one would expect to find in a random group. These observations suggest that many cirrhotic patients who develop diabetes may be genetically predisposed to do so. Far more intriguing is the implication that patients with a predisposition to diabetes may also be unusually susceptible to the development of cirrhosis.

As discussed above, other disorders may lead to the development of secondary diabetes associated with chronic hepatic disease. In his series, Conn reported that several of his patients had pancreatitis, and assumed that those patients with transient diabetes, had diabetes which was secondary to pancreatitis. In at least one patient in this series, the diabetes was thought to be secondary to hemochromatosis.

Conceptually the diabetes of cirrhosis may develop in one of three general eays. First there is diabetes of purely genetic origin, i.e. primary diabetes which would ultimately appear without any of the additional diabetogenic stimuli associated with chronic liver disease.

Secondly, diabetes may develop in those patients with a genetic predisposition in whom diabetogenic stimuli such as pancreatitis or hemosiderosis are present. The association of increased iron absorption with either pancreatitis or PCA for example,(40,41) shows how these

factors may interact. The patient with a positive family history of diabetes who becomes overtly diabetic shortly after PCA, and is also found to have moderately increased iron deposition in the liver on subsequent biopsy may fall into this category. It is conceivable that the hypothetical factor which is responsible for primary diabetes may be potentiated after the construction of a PCA.

Thirdly, patients with chronic liver disease without genetic predisposition to diabetes may develop diabetes as a consequence of discrete organic dysfunction associated with liver disease. Conn found several patients with diabetes and pancreatitis, whose diabetes disappeared within one year thereafter.(5) Pure, irreversible, secondary diabetes may occur with hemosiderosis alone or with chronic fibrosing pancreatitis, in the absence of genetic predisposition.

Having defined diabetes, and having discussed the multitude of variables which may play a role in the development of the diabetes in cirrhosis we can now turn to our data.

Were the Operated and Non-Operated Groups of Patients Truly Similar?

As seen in Table 11 at the time of inclusion into

the study the cirrhosis was approximately equally advanced in the two groups as measured by the similarity of laboratory values and physical signs of the disease. These features were also similar at the end of the period of observation.

Furthermore there was no statistically significant difference in the prevalence of pancreatitis in the two groups. Similarly, the appearance of hemosiderosis was not significantly different between operated and non-operated patients. Neither of these disorders was present in a sizeable fraction of the patients under consideration.

A positive family history of diabetes was found in 20 (27.8%) of 72 patients in the Operated Group as compared with 15 (14.6%) of 103 in the Non-Operated Group. Furthermore, it was observed that of those 20 operated patients with a positive family history, nine (45%) went on to develop diabetes, while only 12 (23%) of the 52 operated patients without a positive family history developed diabetes ($\chi^2 = 2.38$ $p > 0.05$). Conversely, three (20%) of 15 non-operated patients with a positive family history of diabetes developed diabetes compared with 13 (14.8%) of the 88 non-operated patients without family history of diabetes, who developed this disease. These findings suggest that the majority of post-shunt diabetes occurs in cirrhotic patients with a predisposition to diabetes precipitated by some factor which is induced or increased by the creation of the PCA.

Were the Features of Cirrhosis Similar in the Patients with and Without Diabetes?

As seen in Table 12, the features of cirrhosis were similar comparing all diabetic patients with all non-diabetic patients. There was no significant difference in the physical signs of cirrhosis or in the liver function studies. This similarity suggests that no one clinical feature of the cirrhosis was obviously associated with the development of diabetes. A positive family history of diabetes was found in 12 (31.4%) of 37 diabetic patients, compared with 25 (18.1%) of 120 non-diabetic patients. This difference is not statistically significant ($\chi^2 = 1.52$ $p > 0.05$), but again affirms the existence of genetic factors in the development of diabetes.

Was the Diabetes Similar in the Operated and Non-Operated Groups? (Table 13)

The diabetes appears tp be similar in both operated and non-operated diabetic patients. All patients had maturity onset diabetes characterized by fasting hyperglycemia and glycosuria. The mean age of onset of diabetes was similar in the two groups. The diabetes in both groups was mild. About two-thirds of all patients were maintained on dietary therapy alone, and about one-third were treated with tolbutamide. Only one patient in each group was treated with insulin. There was no significant difference in the mode of therapy when comparing the two groups. The frequency of vascular

complications was extremely low and was not significantly greater in either of the groups.

Of operated patients with diabetes, nine (42.8%) had a positive family history as opposed to only 3 (18.7%) of the non-operated patients. Although this difference is not significant, this disparity would seem to indicate that patients with a positive family history of diabetes are more likely to develop diabetes if they have a PCA than if they do not, and that probably the PCA plays a part in accelerating the development of this disease.

<u>What was the Cumulative Incidence of Diabetes?</u>

Figure III shows the cumulative occurrence of diabetes during the follow-up period. The data used in calculating the "life survival" curves as shown in Figure III are shown in Tables 16 and 17. These data indicate that during the first 24 months post PCA, 7 (11.5%) of 67 operated patients considered to be at risk during this period developed diabetes. During this same period, 3 (3.4%) of 88 non-operated patients developed diabetes ($p > 0.05$). Furthermore, of 11 patients who developed diabetes after PCA, 7 (64.0%) did so during the first 24 months post-op, while during the same period only 3 (37.5%) of 8 non-operated patients developed diabetes.

Figure III shows that the cumulative incidence of diabetes in non-operated patients assumes a linear

distribution, with the incidence maintaining a reasonably steady rate throughout the period of follow-up. The distribution of diabetes in the operated patients shows a steep initial rise in the appearance of diabetes from zero to 24 months, followed by a linear pattern which closely parallels the curve of the non-operated patients. This observation suggests that whatever the mechanism of PCA-precipitated diabetes, it apparently acts rapidly on most of its targets.

Of the seven patients who developed diabetes within 24 months of PCA, three had a positive family history of diabetes (not significant), one patient who had a pre-operative history of chronic fibrosing pancreatitis and was observed to have elevated hepatic hemosiderin deposits on biopsy two years post-operatively was also found to have diabetes at that time. In the six other patients who developed diabetes within 24 months, none was found to have evidence of pancreatitis or hemosiderosis. Two patients were found to have diabetes within two months of surgery which persisted throughout the subsequent period of follow-up. In neither case could any significant precipitating factor be identified.

Analysis of Eleven New Cases of Diabetes Post Shunt

Eleven new cases of diabetes were observed after PCA in these studies (Table 15). Analysis of these cases

was undertaken in the hope of determining what factors contributed to the development of the diabetes. These patients developed diabetes from one to 120 months (mean of 20 months) after creation of a PCA. The mean age of onset of diabetes was 45 years. Four of the 11 had a positive family history of diabetes, and three had hemosiderosis. One had pancreatitis and one was found to have a carcinoma of the pancreas. The diabetes in these patients was relatively homogeneous. In most it was mild, without ketosis. Insulin therapy was required in two patients. One patient had peripheral arterial insufficiency requiring amputation. No other patients exhibited arterial insufficiency. Several pathogenetic factors must be considered in these patients.

<u>Deterioration of Liver Function</u>. It is well established that hepatic blood flow falls after construction of portacaval shunts in man.(32) It is also known that in patients with PCA, hepatic failure is the most common cause of death.(35,36) In our patients however, deterioration of liver function after PCA was not consistently a problem. Three patients (P.D., B.R., and J.V.) died of hepatic failure at 116, 56, and 141 months post operatively. These same three had developed diabetes 37, 48, and 120 months respectively post PCA. In none of the cases however, were liver function tests significantly changed from pre-shunt values at the time diabetes was first

recognized. On the other hand liver function improved in several patients after PCA. In general liver function has been found to deteriorate in one third, remain stable in one third, and improve in one third of patients after PCA. Our data in these 11 patients do not implicate failing hepatic function as a precipitating factor in the development of post shunt diabetes.

Hemosiderosis. The full blown hemochromatotic syndrome has been reported to develop rapidly after construction of a portacaval anastomosis.(20) Three of our 11 patients were found to have post shunt hemosiderosis. In all three it is probable that the hemosiderosis played a role in the development of diabetes. In two of these patients (F.B. and B.R.), diabetes and hemosiderosis were first recognized at approximately thr same time, while in the third (J.V.), the hemosiderosis preceeded the onset of diabetes by three years. In the cases of F.B. and B.R. the presence of a persistent hyperlipemia along with the hemosiderosis may also have played a role in the precipitation of diabetes. It is interesting that of the three cases of post shunt hemosiderosis, only one occurred during the period of peak incidence of post shunt diabetes. The other two were noted four and seven years after surgery. Contrastingly, none of the eight patients who developed diabetes soon after inclusion in the Non-Operated Group had hemosiderosis.

<u>Pancreatitis</u>. Only one patient (F.B.), who developed diabetes post-operatively had had overt pancreatitis. He had had a long history of chronic recurrent pancreatitis prior to PCA. Two years after PCA he became diabetic and at the same time was found to have hemosiderosis on liver biopsy. In this case it is not clear which of these factors was primary. Probably all participated. Pancreatitis is the most attractive possibility since pancreatitis is associated with iron absorption and hemosiderosis. There was no evidence of pancreatitis in the other patients, and it would appear that diabetes after PCA can not be related to pancreatitis. It is interesting to note that one patient (W.P.) developed carcinoma of the pancreas which was discovered 114 months after surgery. This patient was found to have persistent fasting hyperglycemia about six months prior to the diagnosis of the carcinoma. In this case the neoplastic invasion of the pancreas was probably responsible for the patient's diabetes.

<u>Kaliopenia</u>. We have found no evidence that potassium depletion is more severe after PCA than before. In fact it was our impression that hypokalemia was much less common in shunted than non-shunted patients. There is no evidence in the literature that potassium depletion is accelerated as a result of PCA. It seems unlikely that the diabetes in these 11 patients can be related to potassium depletion.

What Other Factors Might be Responsible? Five post shunt diabetics were not found to have any recognized diabetogenic factor. Four of the five developed diabetes within 20 months after PCA. In these cases with no identifiable precipitating factor, insulin resistance aggravated by PCA may have played a role in the development of diabetes.

Insulin resistance may be related to shunting of insulin from portal to systemic circulation. Normally about half of the insulin secreted into the portal vein is degraded by the liver during its initial passage through the liver.(42) The resultant hyperinsulinemia might decrease target organ sensitivity by inducing tolerance to insulin which in turn could lead to further insulin production until islet cell exhaustion interrupted this vicious cycle.

While all of our patients both operated and unoperated had spontaneous portal-systemic shunting before surgery, the shunting was increased following PCA. This increased shunting of blood may sufficiently accelerate the shunting of insulin to precipitate islet cell failure.

Islet cell exhaustion may also be brought about through increasing demands for insulin secondary to the shunting of glucose around the liver, although this is probably a much less important factor. In patients with

portal-systemic shunting of blood, orally ingested glucose, a large fraction of which is normally removed in its initial passage through, will bypass the liver and enter the systemic circulation.(43) The post prandial hyperglycemia so produced might further increase the demand for insulin as well as further stimulate the cells to produce insulin.

Paradoxically, a beneficial effect of PCA, has occasionally been observed in patients who already have diabetes. Several observers have reported improvement in glucose tolerance after PCA.(31,44) Conn found that glucose tolerance deteriorated in most cirrhotic patients after PCA, but that in all three cirrhotic patients with diabetes whom he studied, glucose tolerance improved after the shunt.(37) We observed one patient inwhom PCA was followed by a sustained disappearance of hyperglycemia and glycosuria.

The mechanism by which PCA may improve diabetes has been explored by LaVeen and his associates. He demonstrated that Eck fistulae corrected diabetes in dogs rendered diabetic by partial pancreatectomy.(45) Presumably by avoiding hepatic degradation of insulin in its first passage through the liver, Samaan(23) and others have shown that insulin secretion, as determined by serum insulin levels after glucose administration, is greatly increased by PCA. The creation of a portacaval shunt in

a diabetic patient may be equivalent to a sizeable increase in insulin output by the pancreas.

Although it is conceivable that a single mechanism is responsible for post shunt diabetes, it is more likely that this syndrome may arise in a variety of ways. Genetic predisposition plays a role but it is not the only role, or even the major one. Until a reliable genetic marker to detect predisposition to diabetes is found, the genetic aspects of diabetes must remain speculative. Hepatic hemosiderin deposition, which is increased by PCA, seemed to play a role in some patients, but not all. In other patients diabetes may have developed as the result of secondary, non-hepatic, non-shunt related causes such as neoplastic or inflammatory injury or destruction of the islets of Langerhans. The majority of our cases revealed no clues. One must conclude, therefore, that there may be many causes of diabetes after portacaval anastomoses, that these factors may act in concert, and that the critical factor is entirely obscure.

SUMMARY

The association of diabetes with portacaval anastomosis was investigated in a group of 93 cirrhotic patients with PCA. Diabetes was significantly more common (21 of 72 followed 27.8%) in this group than in a control group of non-operated cirrhotic patients (16 of 103, 15.5%) Considering only those patients who developed diabetes after PCA, a similar trend was observed (11 of 62, 17.7% operated vs. 8 of 95, 9.5% control), although this was slightly less significant.

The diabetes in both those with PCA and non-operated controls was maturity onset in type, characterized by fasting hyperglycemia, minimal glycosuria, relative freedom from vascular complications, and simple management with diet or oral agents. Although the features of cirrhosis were similar in operated and non-operated patients a history of diabetes in the immediate family (28% vs. 15%) was far more common among those with PCA.

Analysis of the 11 patients who developed diabetes after PCA revealed that this group was not significantly different from the others in severity of cirrhosis and type of diabetes. Several diabetogenic factors were found to be operative in this group but these were not found to be present to a greater degree than that which was observed in the other groups. These disorders commonly associated with

chronic liver disease could result in diabetes of hepatogenous, pancreatitic, hemosiderotic, kaliopenic, insulin resistant, somatotropic, or genetic origin.

The data suggest that while no single factor can be elucidated, PCA may precipitate diabetes in susceptible patients through the potentiation of a number of disorders commonly associated with cirrhosis and may even by itself induce diabetes de novo in some cirrhotic patients.

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TABLE 1. CASE REPORTS OF DIABETES APPEARING AFTER PORTACAVAL ANASTAMOSES

Author	Ref.	Date	Case	Age	Sex	Interval post-PCA (months)	Proposed Pathogenesis
Hearn, G. W.	1	1963	1	34	F.	5	Pancreatic islet cell exhaustion secondary to chronic over-stimulation
			2	48	M.	18	
Larcan, A., et. al.	2	1965	3	49	M.	19	Pancreatic islet cell exhaustion
Bernardes, P., et. al.	3	1966	4	55	M.	7	Pancreatic disease
			5	40	M.	16	Pancreatic disease
Christensen, M. F.	4	1967	6	41	M.	14	"Possible existence of an insulin stimulating factor in the hepato-portal region."
			7	53	F.	9	

TABLE 2.

PROPHYLACTIC SHUNT STUDY I

GENERAL DATA

GROUP	NO.	AGE	LAENNEC'S CIRRHOSIS	DURATION OF SYMPTOMS (months)
CONTROL	31	49	97%	25 ± 35
PROPHYLACTIC SHUNT	25	51	88%	12 ± 15

LIVER FUNCTION AT TIME OF INCLUSION

GROUP	SERUM BILIRUBIN	BSP	SGOT	SERUM ALBUMIN	AMMONIA TOLERANCE
CONTROL	1.7	28	44	2.8	297
PROPHYLACTIC SHUNT	1.2	25	33	3.0	291

9/1/66

TABLE 3.

TABLE 4.

PROPHYLACTIC SHUNT STUDY I

PORTAL HYPERTENSION

GROUP	NO.	SIZE OF ESOPHAGEAL VARICES	AMMONIA TOLERANCE TEST µg %	SPLENIC PULP PRESSURE cm H_2O
CONTROL	31	2+	232	34
PROPHYLACTIC SHUNT	25	2+	233	31

TABLE 5.

PROPHYLACTIC SHUNT STUDY II

GENERAL DATA

1/1/71

GROUP	NO.	AGE	LAENNEC'S CIRRHOSIS %	DURATION OF SYMPTOMS (months)
CONTROL	22	47	100	33
PROPHYLACTIC SHUNT	19	47	100	24
EXCLUSION (MISCELLANEOUS)	26	57	96	20
EXCLUSION (NON-ASCITIC)	33	51	100	21

TABLE 6. PROPHYLACTIC SHUNT STUDY II

LIVER FUNCTION

ROUP	NO.	SERUM BILIRUBIN	THYMOL TURBIDITY	ALKALINE PHOSPHATASE	SGO TRANSAMINAS
ONTROL	22	1.4	3.7	4.8	45
ROPHYLACTIC HUNT	19	1.5	3.9	3.8	42
XCLUSION MISCELLANEOUS)	26	1.3	3.8	4.5	50
XCLUSION ION-ASCITIC)	33	1.5	3.4	4.7	82

TABLE 7.

PROPHYLACTIC SHUNT STUDY II

PORTAL HYPERTENSION

1/1/71

GROUP	NO.	SIZE OF ESOPHAGEAL VARICES	AMMONIA TOLERANCE TEST μg %	SPLENIC PULP PRESSURE cm H_2O
CONTROL	22	2.4+	352	36
PROPHYLACTIC SHUNT	19	2.4+	326	35
EXCLUSION (MISCELLANEOUS)	26	2.1+	335	27
EXCLUSION (NON-ASCITIC)	33	1.7+	239	—

TABLE 8

INCIDENCE OF DIABETES
PORTACAVAL SHUNT STUDY I

	NO. PTS. AT INCLUSION	NO. DIABETICS (%)	NO. PATIENTS FOLLOWED	MEAN FOLLOW-UP (MOS.)	NO. DIABETICS BEGINNING OF FOLLOW-UP (%)	NO. DIABETICS AT END OF FOLLOW-UP (%)	NO. NEW DIABETICS (%)
CONTROL I	31	2 (6.5)	28	72.1	2 (7.2)	5 (17.9)	3 (10.7)
EXCLUSION I	8	2 (2.5)	7	66.2	1 (14.4)	2 (28.4)	1 (14.2)
REFUSAL I	4	0 (0)	4	63.7	0 (0)	1 (25.0)	1 (25.0)
TOTAL NON OPERATED I	43	4 (9.3)	39	68.7	3 (7.7)	8 (20.5)	5 (12.8)
PROPHYLACTIC SHUNTS I	25	0 (0)	20	50.1	0 (0)	5 (25.0)	5 (25.0)

TABLE 9

INCIDENCE OF DIABETES
PORTACAVAL SHUNT STUDY II

GROUP	NO PTS. AT INCLUSION	NO. DIABETICS (%)		NO PATIENTS FOLLOWED	MEAN FOLLOW-UP (MOS.)	NO. DIABETICS BEGINNING OF FOLLOW-UP (%)		NO. DIABETICS AT END OF FOLLOW-UP (%)		NO. NEW DIABETICS (%)	
CONTROL II	21	1	(4.7)	17	28.4	0	(0)	1	(5.9)	1	(5.9)
EXCLUSION II	26	0	(0)	18	32.4	0	(0)	2	(11.1)	2	(11.1)
REFUSAL II	2	0	(0)	2	26.8	0	(0)	0	(0)	0	(0)
NON-ASCITIC	29	5	(17.2)	27	26.1	5	(18.5)	5	(18.5)	0	(0)
TOTAL NON OPERATED II	78	6	(7.7)	64	26.8	5	(7.8)	8	(12.5)	3	(4.7)
PROPHYLACTIC SHUNTS II	20	3	(15.0)	16	26.2	3	(18.7)	4	(25.0)	1	(6.3)

TABLE 10

INCIDENCE OF DIABETES
ALL GROUPS COMBINED

GROUP	AT INCLUSION		DURING FOLLOW-UP				
	NO. PATIENTS AT INCLUSION	NO. DIABETICS (%)	NO. PATIENTS FOLLOWED	MEAN FOLLOW-UP (MOS.)	NO. DIABETICS BEGINNING OF FOLLOW-UP(%)	NO. DIABETICS AT END OF FOLLOW-UP(%)	NO. NEW DIABETICS (%)
CONTROL I-II	52	3 (5.8)	45	44.5	2 (4.4)	6 (13.3)	4 (8.9)
EXCLUSION I-II	34	2 (5.9)	25	41.9	1 (4.0)	4 (16.0)	3 (12.0)
REFUSAL I-II	6	0 (0)	6	51.0	0 (0)	1 (16.7)	1 (16.7)
NON ASCITIC	29	5 (17.2)	27	26.1	5 (18.5)	5 (18.5)	0 (0)
TOTAL NON-OPERATED	121	10 (8.3)	103	44.5	8 (7.8)	16 (15.5)	8 (7.8)
PROPHYLACTIC SHUNTS I-II	45	3 (6.6)	36	49.0	3 (8.3)	9 (25.0)	6 (16.7)
THERAPEUTIC SHUNTS	48	8 (16.7)	36	30.5	7 (19.5)	12 (33.0)	5 (13.9)
TOTAL OPERATED	93	11 (11.8)	72	39.8	10 (12.5)	21 (27.8)	11 (15.3)

TABLE 11. COMPARISON OF FEATURES OF CIRRHOSIS IN OPERATED AND NON-OPERATED GROUPS AT THE TIME OF INCLUSION

Finding	Non-Operated	Operated	Statistical Significance
No. of patients followed	103	72	
Mean age at inclusion (yrs.)	51.0	50.5	N.S.*
Family history of diabetes	15 (14.6%)	20 (27.8%)	$\chi^2 = 3.84$ $p < 0.05$
Physical signs of Cirrhosis			
Hepatomegaly	97.5%	98.5%	N.S.
Splenomegaly	47.5%	41.5%	N.S.
Jaundice	48.0%	44.0%	N.S.
Spider angiomata	64.0%	66.7%	N.S.
Ascites	64.5%	66.7%	N.S.
Liver Function Studies			
Serum albumin (g/%)	2.8	3.0	N.S.
SGOT (Reitman-Frankel units)	52.0	47.5	N.S.
Alkaline phosphatase (King Armstrong units)	14.7	13.5	N.S.

*N.S. = Not significant

TABLE 12. COMPARISON OF CLINICAL FEATURES OF CIRRHOSIS IN DIABETIC AND NON-DIABETIC PATIENTS

Clinical Feature	Diabetic	Non-Diabetic	Statistical Significance
No. of pts. followed	37	138	
Mean age at inclusion	52.5	50.5	N.S.*
Family history of diabetes	12 (31.4%)	25 (18.1%)	N.S.
Physical Findings prior to inclusion			
Spider Angiomata	32.6%	45.3%	N.S.
Ascites	47.0%	66.0%	N.S.
Hepatomegaly	100.0%	97.5%	N.S.
Splenomegaly	53.2%	42.7%	N.S.
Liver Function Studies			
Serum Albumin (g/%)	3.1	2.9	N.S.
SGOT (Reitman-Frankel units)	46.5	50.5	N.S.
Alkaline Phosphatase (King Armstrong units)	14.3	17.0	N.S.

*N.S. = Not Significant

TABLE 13. COMPARISON OF CLINICAL FEATURES OF DIABETES IN OPERATED-DIABETIC AND NON-OPERATED DIABETIC PATIENTS

Finding	Operated Diabetic	Non-Operated Diabetic	Statistical Significance
No. of diabetic patients	21	16	N.S.*
Mean age at inclusion (years)	52.0	53.0	N.S.
Mean age at onset of diabetes (years)	51.0	54.5	N.S.
Family history of diabetes	9 (42.8%)	3 (18.7%)	N.S.
Pancreatitis	1 (4.8%)	1 (6.2%)	N.S.
Hepatic Hemosiderosis	4 (19.0%)	0 (0%)	N.S.
Glycosuria	18 (83.3%)	14 (87.5%)	N.S.
Transient diabetes	1 (4.8%)	2 (13.3%)	N.S.
Therapy employed			
Insulin	2 (16.7%)	1 (6.2%)	N.S.
Tolbutamide	7 (33.3%)	3 (20.0%)	N.S.
Diet only	13 (62.0%)	12 (75.0%)	N.S.

*N.S. = Not Significant

TABLE 14. COMPARISON OF PREVALENCE OF PANCREATITIS AND HEMOSIDEROSIS IN VARIOUS SUBGROUPS

	No. of pts. followed	No. and percentage of pts. with pancreatitis	Statistical Significance	No. and percentage of pts. with hemosiderosis	Statistical Significance
Operated	72	6 (8.3%)	N.S.*	4 (5.6%)	N.S.
Non-Operated	103	4 (3.9%)		3 (2.9%)	
Diabetic	37	2 (5.4%)	N.S.	4 (10.8%)	$\chi^2 = 3.64$ $p < 0.05$
Non-Diabetic	138	8 (5.8%)		3 (2.2%)	
Operated Diabetic	21	1 (4.8%)	N.S.	4 (19.0%)	N.S.
Non-Operated Diabetic	16	1 (6.2%)		0 (0.0%)	

*N.S. = Not Significant

TABLE 15

ANALYSIS OF POST PCA DIABETIC PATIENTS

PT.	TYPE OF CIRRHOSIS	AGE OF ONSET OF DIABETES	ONSET (MONTHS) POST PCA DIABETES	FAMILY HISTORY DIABETES	DIABETIC THERAPY	PANCRE-ATITIS	HEMO-SIDEROSIS	DEATH (MONTHS) POST PCA	CAUSE OF DEATH	POSSIBLE CONTRIBUTING DIABETOGENIC FACTORS
F.B.	L.C.	37	24	+	I,T	+	+	65	PNEUMONIA	GENETIC, PANCREATITIS HEMOSIDEROSIS
S.C.	L.C.	56	20	+	D	0	0	29	CHEST INJURY	GENETIC
P.D.	L.C.	49	2	0	T	0	0	116	HEPATO-RENAL FAILURE	-
M.K.	L.C.	49	8	0	I,T	0	0	58	? CVA	-
C.M.	L.C.	44	18	+	D	0	0	0		GENETIC
W.P.	L.C.	64	108	0	D	0	0	114	CARCINOMA PANCREAS	CARCINOMA OF PANCREAS
J.R.	L.C.	44	1	0	T	0	0	0		-
F.R.	L.C.	47	72	0	T	0	0	0		-
B.R.	L.C.	49	48	0	D	0	+	56	HEPATIC FAILURE	HEMOSIDEROSIS
C.S.	L.C.	63	20	0	D	0	0	41	CARCINOMA COLON	-
J.V.	P.N.C.	45	120	+	D	0	+	141	HEPATIC FAILURE	GENETIC HEMOSIDEROSIS

LEGEND: L.C.= LAENNEC'S CIRRHOSIS
P.N.C.= POST-NECROTIC CIRRHOSIS

I= INSULIN
T= TOLBUTAMIDE
D= DIET ALONE

+ = PRESENT
0 = ABSENT
- = UNKNOWN

TABLE 16

DATA USED IN CALCULATING THE CUMULATIVE INCIDENCE OF DIABETES AFTER INCLUSION NON- OPERATED PATIENTS

INTERVAL (MOS.) POST PCA	NO. AT RISK AT 0 TIME	NO. AT RISK DURING NEXT PD.	NO. WHO DROP OUT	NO. WHO DEVELOP DIABETES	% WHO DEVELOP DIABETES	% WHO DO NOT DEVELOP DIABETES	CUMULATIVE% OF PTS. WITHOUT DIABETES	CUMULATIVE % OF PTS. WITH DIABETES
0	121	121	0	10	8.3	91.7	91.7	8.3
0-6	111	103.5	15	1	0.9	99.1	91.0	9.0
7-12	95	88.5	13	0	0	100	91.0	9.0
13-18	82	77	10	2	2.6	97.4	88.6	11.4
19-24	70	66.5	7	0	0	100	88.6	11.4
25-30	63	61.5	3	0	0	100	88.6	11.4
31-36	60	58	4	0	0	100	88.6	11.4
37-42	56	55.5	1	0	0	100	88.6	11.4
43-48	55	54	2	2	3.7	96.3	88.5	14.5
49-54	51	51	0	1	2.0	98.0	84.0	16.0
55-60	50	48	4	0	0	100	84.0	16.0
61-66	46	45.5	1	0	0	100	84.0	16.0
67-72	45	44.5	1	1	2.2	97.8	82.2	17.8
73-78	43	42.5	1	0	0	100	82.2	17.8
79-84	42	42	0	0	0	100	82.2	17.8
85-90	42	42	0	0	0	100	82.2	17.8
91-96	42	42	0	0	0	100	82.2	17.8
97-102	42	42	0	1	2.4	97.6	80.0	20.0
103-108	41	40.5	1	0	0	100	80.0	20.0
108-	40	39	2	0	0	100	80.0	20.0

TABLE 17

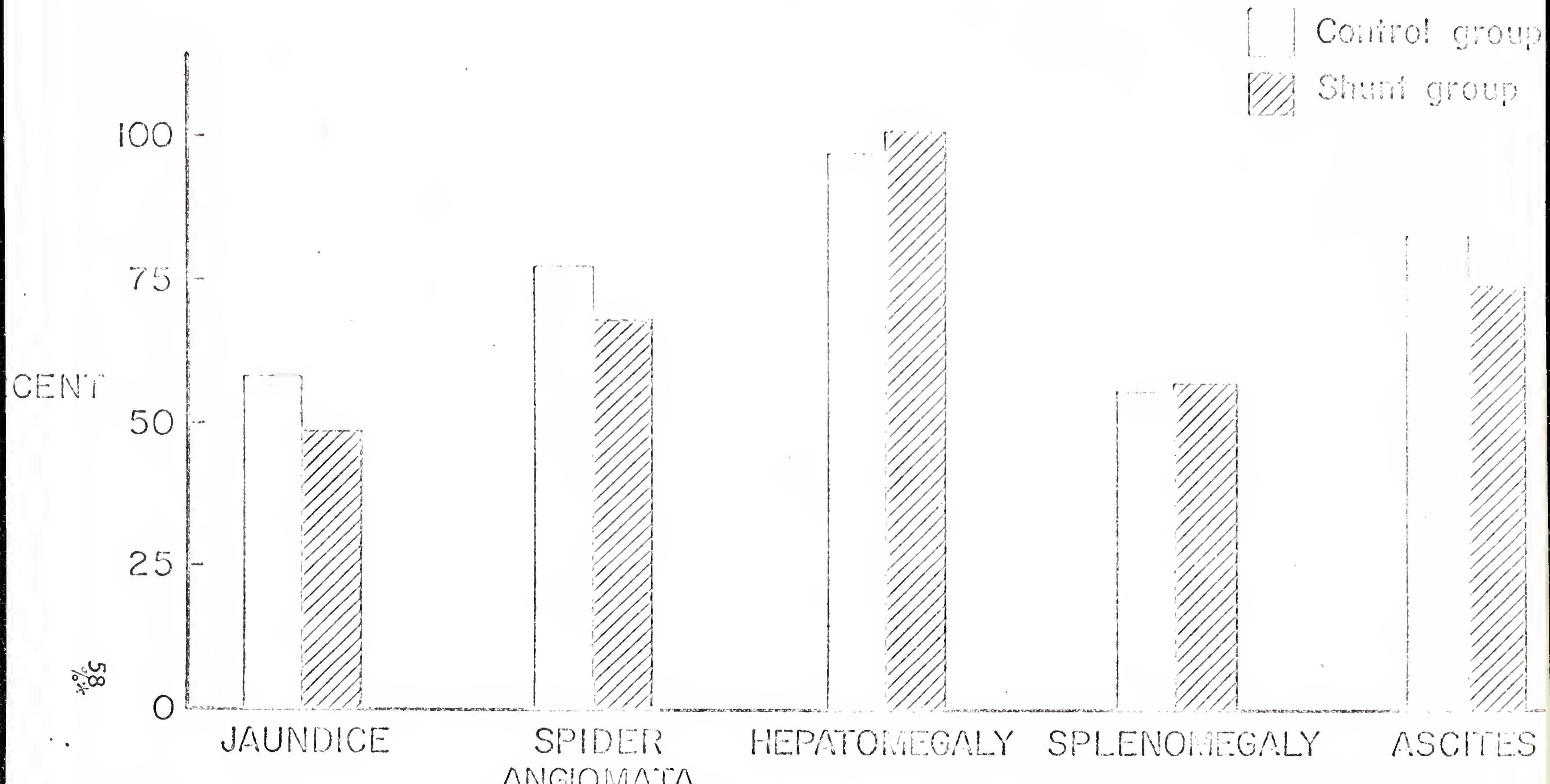
DATA USED IN CALCULATING THE CUMULATIVE INCIDENCE OF DIABETES AFTER PCA OPERATED PATIENTS

INTERVAL (MOS.) POST PCA	NO. AT RISK AT 0 TIME	NO. AT RISK DURING NEXT PD.	NO. WHO DROP OUT	NO. WHO DEVELOP DIABETES	% WHO DEVELOP DIABETES	% WHO DO NOT DEVELOP DIABETES	CUMULATIVE% OF PTS. WITHOUT DIABETES	CUMULATIVE % OF PTS. WITH DIABETES
0	93	93	0	11	11.8	88.2	88.2	11.8
0-6	82	71.5	21	1	1.4	98.6	87.0	13.0
7-12	60	59	2	3	5.1	94.9	82.5	17.5
13-18	54	52	4	1	1.9	98.1	81.0	19.0
19-24	49	47.5	3	2	4.2	95.8	78.0	22.0
25-30	44	44	0	0	0	100	78.0	22.0
31-36	44	42.5	3	0	0	100	78.0	22.0
37-42	41	38	6	0	0	100	78.0	22.0
43-48	35	33.5	3	1	3.0	97.0	75.5	24.5
49-54	31	29	4	0	0	100	75.5	24.5
55-60	27	26	2	0	0	100	75.5	24.5
61-66	25	24.5	1	0	0	100	75.5	24.5
67-72	24	23	2	1	4.3	95.7	72.5	27.5
73-78	21	21	0	0	0	100	72.5	27.5
79-84	21	21	0	0	0	100	72.5	27.5
85-90	21	21	0	0	0	100	72.5	27.5
91-96	20	19.5	1	0	0	100	72.5	27.5
97-102	19	19	0	0	0	100	72.5	27.5
103-108	19	19	0	1	5.3	94.7	69.0	31.0
108-	18	16	4	1	6.3	93.7	65.0	35.0

PROPHYLACTIC SHUNT STUDY I

PHYSICAL FINDINGS

FIGURE I



58%*

PHYSICAL SIGNS OF CIRRHOSIS AT TIME OF ADMISSION TO HOSPITAL—STUDY II 1/1/71

FIGURE II

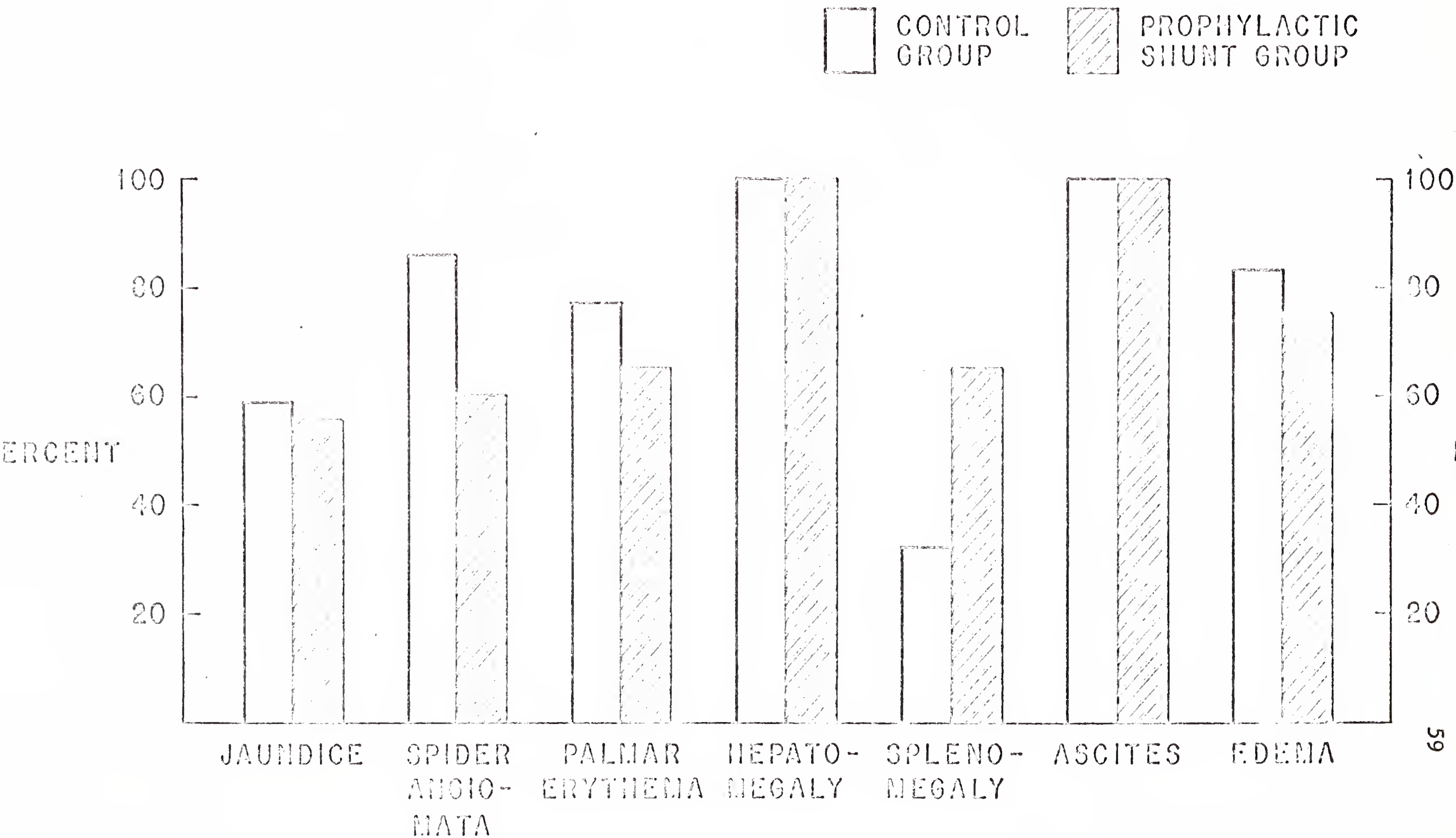
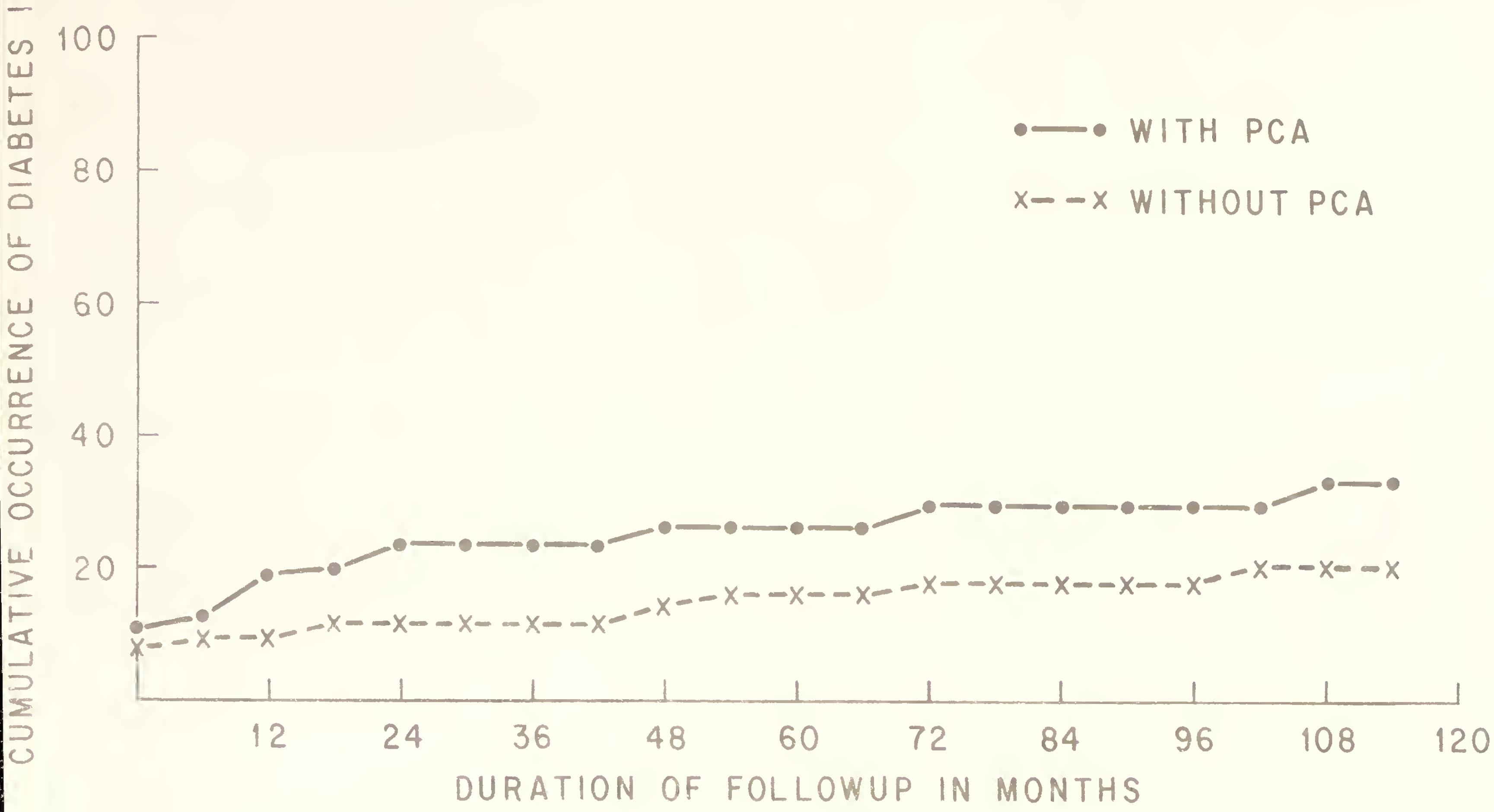


FIGURE III

CUMULATIVE OCCURRENCE OF DIABETES IN PATIENTS WITH AND WITHOUT PORTACAVAL ANASTOMOSIS (PCA)



APPENDIX A. DATA COLLECTION SHEET

NAME HOSP. NO. AGE SEX STUDY NO.

HISTORY	DATES
Alcholic	Date of inclusion
Diabetes	Date of shunt
Pancreatitis	Latest study
Hemochromatosis	Onset of cirrhosis
	Onset of diabetes

EVIDENCE OF CIRRHOSIS	BEFORE SHUNT	AFTER SHUNT
Hepatomegaly		
Splenomegaly		
Ascites		
Jaundice		
Chest hair		
Gynecomastia		
Palmar erythemia		
Spider angiomata		

LAB DATA	BEFORE	AFTER
Bilirubin		
Thymol		
Alk. Phosphatase		
SGOT		
Total Pro.		
Albumin		
Amylase		
Lipase		
Iron		
IBC		
Pro time		

CARBOHYDRATE TOLERANCE STUDIES	BEFORE	AFTER
FBS		
GTT		
ATT		
Urine		

LIVER BIOPSY

SPLENOPORTOGRAM

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